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I also certify that by virtue of an assignment registered under the Patents Act 1977, the application is now proceeding in the name as substituted.

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Signed P. Mahoney

Dated 22 November 2000

GB0000313.7

By virtue of a direction given under Section of the Patents Act 1977, the application is proceeding in the name of

ASTRAZENECA AB,
Incorporated in Sweden,
S-151 85 Sodertalje,
Sweden

[ADP No. 07822448003]

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1. **Your reference** — PHM 99-154

2. **Patent application number** *(The Patent Office will fill in this part)* — 0000313.7

10JAN00 E503670-1 002934
P01/7700 0.00-0000313.7

3. **Full name, address and postcode of the or of each applicant** *(underline all surnames)*

AstraZeneca UK Ltd
15 Stanhope Gate
LONDON W1Y 6LN
Great Britain

SECTION 30 (1) APPLICATION FILED 6.7.00

Patents ADP number *(if you know it)* — ~~6254007002~~ 7810294001

If the applicant is a corporate body, give the country/state of its incorporation

4. **Title of the invention** — FORMULATION

5. **Name of your agent** *(if you have one)* — BROWN, Andrew Stephen

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

Global Intellectual Property
AstraZeneca PLC
Mereside, Alderley Park
Macclesfield Cheshire, SK10 4TG
Great Britain

Patents ADP number *(if you know it)* — 7259252002

6. **If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and** *(if you know it)* **the or each application number**

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. **If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application**

Number of earlier application	Date of filing *(day / month / year)*

8. **Is a statement of inventorship and of right to grant of a patent required in support of this request?** *(Answer 'Yes' if:*
a) any applicant named in part 3 is not an inventor, or
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c) any named ...

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Claim(s)	2
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Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*

Request for preliminary examination and search *(Patents Form 9/77)*

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Any other documents *(please specify)*

11. I/We request the grant of a patent on the basis of this application.

Signature J M Marshall

Date 10-Jan-2000

12. Name and daytime telephone number of person to contact in the United Kingdom

Mrs Joanne M Marshall - 01625 516485

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FORMULATION

The invention relates to a novel sustained release pharmaceutical formulation adapted for administration by injection containing the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol, more particularly to a formulation adapted for administration by injection containing the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol in solution in a ricinoleate vehicle which additionally comprises at least one alcohol and benzyl benzoate.

Oestrogen deprivation is fundamental to the treatment of many benign and malignant diseases of the breast and reproductive tract. In premenopausal women, this is achieved by the ablation of ovarian function through surgical, radiotherapeutic, or medical means, and, in postmenopausal women, by the use of aromatase inhibitors.

An alternative approach to oestrogen withdrawal is to antagonise oestrogens with antioestrogens. These are drugs that bind to and compete for oestrogen receptors (ER) present in the nuclei of oestrogen-responsive tissue. Conventional nonsteroidal antioestrogens, such as tamoxifen, compete efficiently for ER binding but their effectiveness is often limited by the partial agonism they display, which results in an incomplete blockade of oestrogen-mediated activity (Furr and Jordan 1984, May and Westley 1987).

The potential for nonsteroidal antioestrogens to display agonistic properties prompted the search for novel compounds that would bind ER with high affinity without activating any of the normal transcriptional hormone responses and consequent manifestations of oestrogens. Such molecules would be "pure" antioestrogens, clearly distinguished from tamoxifen-like ligands and capable of eliciting complete ablation of the trophic effects of oestrogens. Such compounds are now referred to as Selective Estrogen Receptor-Downregulators (SERDs). The rationale for the design and testing of novel, pure antioestrogens has been described in: Bowler et al 1989, Wakeling 1990a, 1990b, 1990c. Wakeling and Bowler 1987, 1988.

Steroidal analogues of oestradiol, with an alkylsulphinyl side chain in the 7α position, provided the first examples of compounds devoid of oestrogenic activity (Bowler et al 1989). One of these, 7α-[9-(4,4,5,5,5-pentafluoropentyl sulphinyl)nonyl]oestra-1,3,5-(10)triene-3,17β-diol was selected for intensive study on the basis of its pure oestrogen antagonist

activity and significantly increased antioestrogenic potency over other available antioestrogens. *In vitro* findings and early clinical experience with 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3-5(10)-triene-3,17β-diol have promoted interest in the development of the drug as a therapeutic agent for oestrogen-dependent indications such as breast cancer and certain benign gynaecological conditions.

7α-[9-(4,4,5,5,5-Pentafluoropentylsulphinyl)nonyl]oestra-1,3-5(10)-triene-3,17β-diol, or ICI 182,780, has been allocated the international nonproprietory name fulvestrant, which is used hereinafter. When referring to fulvestrant we include pharmaceutically-acceptable salts thereof and any possible solvates of either thereof.

Fulvestrant binds to ER with an affinity similar to that of oestradiol and completely blocks the growth stimulatory action of oestradiol on human breast cancer cells *in vitro*; it is more potent and more effective than tamoxifen in this respect. Fulvestrant blocks completely the uterotrophic action of oestradiol in rats, mice and monkeys, and also blocks the uterotrophic activity of tamoxifen.

Because fulvestrant has none of the oestrogen-like stimulatory activity that is characteristic of clinically available antioestrogens such as tamoxifen or toremifene, it may offer improved therapeutic activity characterised by more rapid, complete, or longer-lasting tumour regression; a lower incidence or rate of development of resistance to treatment; and a reduction of tumour invasiveness.

In intact adult rats, fulvestrant achieves maximum regression of the uterus at a dose which does not adversely affect bone density or lead to increased gonadotrophin secretion. If also true in humans, these findings could be of extreme importance clinically. Reduced bone density limits the duration of oestrogen-ablative treatment for endometriosis. Fulvestrant does not block hypothalamic ER. Oestrogen ablation also causes or exacerbates hot flushes and other menopausal symptoms; fulvestrant will not cause such effects because it does not cross the blood-brain barrier.

European Patent Application No. 0 138 504 discloses that certain steroid derivatives are effective antioestrogenic agents. The disclosure includes information relating to the preparation of the steroid derivatives. In particular there is the disclosure within Example 35 of the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol, which compound is specifically named in Claim 4. It is also

disclosed that the compounds of that invention may be provided for use in the form of a pharmaceutical composition comprising a steroid derivative of the invention together with a pharmaceutically-acceptable diluent or carrier. It is stated therein that the composition can be in a form suitable for oral or parenteral administration.

Fulvestrant shows, along with other steroidal based compounds, certain physical properties which make formulation of these compounds difficult. Fulvestrant is a particularly lipophilic molecule, even when compared with other steroidal compounds, and its aqueous solubility is extremely low at around 10 $ngml^{-1}$ (this is an estimate from a water/solvent mixture solute since measurements this low could not be achieved in a water only solute).

Currently there are a number of sustained release injectable steroidal formulations which have been commercialised. Commonly these are formulations use oil as a solvent and wherein also additional excipients may be present. Below in Table 1 are described a few commercialised sustained release injectable formulations.

Table 1 - OIL BASED LONG - ACTING INTRAMUSCULAR INJECTIONS

PRODUCT NAME	STEROID	DOSE	TYPE	COMPANY	SOURCE	OIL	BzBz	BzOH	EtOH	DOSE	FREQUENCY
SUSTANON 100			Androgen	Organon	ABPI Data Sheet Comp.	Arachis oil		*10%		1ml	2 weeks
PROLUTON DEPOT	Hydroxy-progesterone hexanoate		Progestogen	Shering HC	ABPI Data Sheet Comp.	Castor oil	up to 46%			1-2ml	1 week
TOCOGESTAN			Progestogen	Theramax	Dict. Vidal	Ethyl oleate	*40%			2ml	< 1week
TROPHOBOLENE			Mixed	Theramax	Dict. Vadal	Olive oil	*45%			1ml	2 - 4 weeks
NORISTERAT			Contraceptive	Schering HC	ABPI Data Sheet Comp.	Castor Oil	YES			1ml	8 weeks
BENZO-GYNOESTRYL			Estradiol	Roussel	Dict. Vidal	Arachis Oil		YES	YES	1ml	1 week
PROGESTERONE -RETARD			Progestogen	Pharlon	Dict. Vidal	Castor Oil	YES			2ml	1 week
GRAVIBINAN			Mixed	Schering HC	Dict. Vidal	Castor Oil	YES			1-2ml	1 - 2 weeks
PARABOLAN			Androgen	Negma	Dict. Vidal	Arachis oil		*5%	*3%	1.5ml	2 weeks
DELESTROGEN	Estradiol valerate	20mg/ml 40mg/ml	Estrodiol	BMS	J.Pharm. Sci (1964) 53(8) 891	Castor Oil	78% 58%	20% 40%	2% 2%		
DELALUTIN	17-Hydroxy progesterone	250mg/ml	Progestrogen	DMS	J.Pharm. Sci.(1964) 53(8) 891	Castor Oil	YES	YES	up to 2%		

BzBz = benzylbenzoate BzOH = benzylalcohol EtOH = ethanol Dict. Vidal = Dictionnaire Vidal
% are w/v and * are approximate as measured directly from a single sample

In the formulations within Table 1 a number of different oils are used to solubilise the compound and additional excipients such as benzybenzoate, benzyl alcohol and ethanol have been used, also volumes of oil needed to solubilise the steroid active ingredient are low. Extended release is achievable for periods from 1 to 8 weeks with the above commercial formulations.

Below in Table 2 is a list showing the solubility of fulvestrant in a number of different solvents.

Table 2 - SOLUBILITY OF FULVESTRANT

SOLVENT	SOLUBILITY ($mgml^{-1}$ at 25°C)
Water	0.001
Arachis oil	0.45
Sesame oil	0.58
Castor oil	~20*
Miglyol 810	3.06
Miglyol 812	2.72
Ethyl oleate	1.25
Benzyl benzoate	6.15
Isopropyl myristate	0.80
Span 85 (surfactant)	3.79
Ethanol	>200
Benzyl Alcohol	>200

* castor oil varies according to supplier and also may vary between batches

As can be seen fulvestrant is significantly more soluble in castor oil than any of the other oils tested. The greater solvating ability of castor oil for steoidal compounds is known and is attributed to the high number of hydroxy groups of riconoleic acid, which is the major constituent of the fatty acids within the triglycerides present in castor oil - see (Riffkin et.al. J. Pharm. Sci., (1964), 53, 891).

However, even when using the best oil based solvent, castor oil, we have found that it is not possible to dissolve fulvestrant in an oil based solvent alone so as to achieve a high enough concentration to dose a patient in a single injection and achieve a therapeutically significant release rate. To achieve a therapeutically significant release rate the amount of fulvestrant needed would require the formulation volume to be large, at least 10 ml. This requires the doctor to inject an excessively large volume of formulation to adminster a dose significantly high enougth for human therapy.

Currently guidelines recommend that no more than 5mls of liquid is injected intramuscularly in a single injection. Pharmacologically active doses required for a 1 month long acting depot formulation of fulvestrant is around 250mg. Therefore, when dissolved in just castor oil fulvestrant would need to be administered in at least 10ml of castor oil, far exceeding the above guidelines, and would have to be administered as two seperate injections.

The addition of organic solvents in which fulvestrant is freely soluble, and which are miscible with castor oil, may be used, such as an alcohol. With the addition of high concentrations of an alcohol concentrations of >50mgml^{-1} of fulvestrant in a castor oil formulation is achievable, thereby giving an injection volumes of <5ml - see Table 3 below.

It is desired to maintian only the minimum amount of excipients necessary for the preformance of the formulation. In Japan injectable formulations containing high concentrations of ethanol may not be approved for sale since a significant number of Japanese are intolerant to ethanol. In addition within Muslin countries high ethanol containing products may not be culturally acceptable. Therefore, there is a need to minimise the amount of alcohols present within such parenteral formulations.

We have surprisingly found that the introduction of benzyl benzoate to the castor oil allows the amount of alcohol needed to solubilise fulvestrant into a concentration of at least 50 mgml^{-1} to be significantly reduced - see Table 3 below. The finding is surprising since the solubility of fulvestrant in benzylbenzoate - see Table 2 above - is significantly lower than the solubility of fulvestrant in an alcohol. The solubility of fulvestrant is also lower in benzyl benzoate than the solubility of fulvestrant in castor oil.

Therefore, we present as a feature of the invention a pharmaceutical formulation adapted for intra-muscular injection comprising fulvestrant, 25% or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 10% weight of benzyl benzoate per volume of formulation and a sufficient amount of a ricinoleate vehicle, taking

into account the addition of any further optional pharamaceutically-acceptable excipients, so as to prepare a formulation of at least 45mgml^{-1} of fulvestrant.

Preferred pharmaceutical formulations of the invention are as described above wherein.

1. The total volume of the formulation is 5ml, or less, and the concentration of fulvestrant is at least 45mgml^{-1}.

2. The total amount of fulvestrant in the formulation is 250mg, or more, and the total volume of the formulation is 5ml, or less.

3. The total amount of fulvestrant in the formulation is 250mg and the total volume of the formulation is 5ml.

Preferred concentrations of a pharmaceutically-acceptable alcohol present in any of the above formulations are; at least 10% w/v, 11% w/v, 12% w/v, 13% w/v, 14% w/v, 15% w/v and, preferably, at least 16% w/v. Maximal concentrations of pharmaceutically-acceptable alcohol present in the formulation are ; 22% w/v or less, 20% w/v or less and 18%w/v or less.

The pharmaceutically-acceptable alcohol may consist of one alcohol or a mixture of two or more alcohols, preferably a mixture of two alcohols. Preferred pharmaceutically-acceptable alsohols for parenteral administration are ethanol, benzyl alcohol or a mixture of both ethanol and benzyl alcohol, preferably the ethanol and benzyl alcohol are present in the formulation in the same w/v amounts. Preferably the formulation alcohol contains 10% w/v ethanol and 10% w/v benzyl alcohol.

It will be understood by the skilled person that the pharmaceutically-acceptable alcohol will be of a quality such that it will meet pharmacopoeial standards (such as are described in the US, British, European and Japanese pharmacopoeias) and as such will contain some water and possibley other organic solvents, for example alcohol in the US Pharmacopeia contains not less than 94.9% by volume and not more than 96.0% by volume of ethanol when measured at 15.56°C. Dehydrated alcohol in the US Pharmacopeia contains not less than 99.5% ethanol by volume when measured at 15.56°C.

Preferred concentrations of benzyl benzoate present in any of the above formulations are; at least 10% w/v, 11% w/v, 12% w/v, 13% w/v, 15% w/v, 16% w/v, 17% w/v, 18% w/v, 19% w/v and 20% w/v. Maximal concentrations of benzyl benzoate are; 60% w/v or less, 50%w/v or less, 45% w/v or less, 40% w/v or less, 35% w/v or less, 30% w/v or less and 25% w/v or less. A preferred concentration is 15% w/v.

It will be understood by the skilled person that the benzyl benzoate will be of a quality that it will meet pharmacopeial standards (such as described in the US, British, European and Japanese pharmacopoeias).

By the use of the term ricinoleate vehicle we mean an oil which has as a majority proportion (at least 50%, 60%, 70%, 80%, 90% or 95% w/v) of its composition as triglycerides of ricinoleic acid. Conveniently the ricinoleate vehicle is castor oil, ideally of pharmacopoeial standards, as described above.

We have surprisingly found that the above formulations of the invention provide, after intra-muscular injection, satisfactory release of fulvestrant over an extended period of time.

This finding is indeed surprising for the following reasons.

1. Previously tested by the applicants have been intra-muscular injections of fulvestrant in the form of an aqueous suspension. We have found extensive local tissue irritation at the injection site as well as a poor release profile. It is believed that the tissue irritation/inflamation was due to the presence of fulvestrant in the form of solid particles. The release profile appeared to be controlled by the extent of inflammation/irritation present at the injection site and therefore diffficult to control. Also the fulvestrant release rate was not sufficiently high to be clinically significant.

2. Our findings from studies using ^{14}C labelled benzyl alcohol show that it dissipates rapidly from the injection site and is removed from the body within 24 hours of administration.

It would be expected that ethanol will dissipate at least as quickly, if not more rapidly, from the injection site.

It is known that benzyl benzoate is metabolised by conjugation to glycine to form hippuric acid by the human liver and excreted into the urine - Martindale: The Extra Pharmacopoeia 32nd edition page 1103, and, therefore, it is unlikely that the benzyl benzoate is always present at the injection site during the extended release period.

We have found that despite the rapid elimination of the additional solubilising excipients, i.e. the alcohol and benzyl benzoate, from the formulation vehicle and the site of injection after injection of the formulation, extended release at therapeutically significant levels of fulvestrant over an extended period is still achieved.

By use of the term "therapeutically significant levels" we mean that blood plasma concentrations of at least 2.5 $ngml^{-1}$, idealy at least 3 $ngml^{-1}$ and no more than 8.5 $ngml^{-1}$ of fulvestrant are achieved in the patient.

By use of the term "extended release" we mean at least two weeks, at least three weeks, and, preferably at least four weeks of continuous release of fulvestrant is achieved. In a preferred feature extended release is achieved for 32 days $\pm$ 4 days.

Therefore we present as a further feature of the invention an extended release pharmaceutical formulation adapted for intramuscular injection comprising fulvestrant, 25% or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 10% weight of benzyl benzoate per volume of formulation and sufficient amount of a ricinoleate vehicle, taking into account the addition of any further optional pharmaceutically-acceptable excipients, so as to prepare a formulation of at least 50$mgml^{-1}$ of fulvestrant.

As described above fulvestrant is useful in the treatment of oestrogen-dependent indications such as breast cancer and gynaecological conditions, such as endometriosis.

Table 3 shows the solubility of fulvestrant in a castor oil vehicle additionally containing alcohols ethanol and benzyl alcohol with or without benzyl benzoate. The results clearly show the positive effect of benzyl benzoate on fulvestrant solubility in castor oil, despite fulvestrant having a lower solubility in benzyl benzoate than in either alcohol or castor oil.

Table 3

Table 3 - EFFECT OF BENZYL BENZOATE ON FULVESTRANT SOLUBILITY IN CASTOR OIL AT 25°C

				% w/v				
Ethanol (96%)	5	5	10	10	10	10	15	15
Benzyl Alcohol	5	5	5	5	10	10	15	15
Benzyl Benzoate		15		15		15		15
Castor Oil	to 100	to100	to 100	to 100	to 100	to 100	to 100	to 100
Fulvestrant Solubility [$mgml^{-1}$]	27	36	46	54	45	65	76	102

Formulation Example

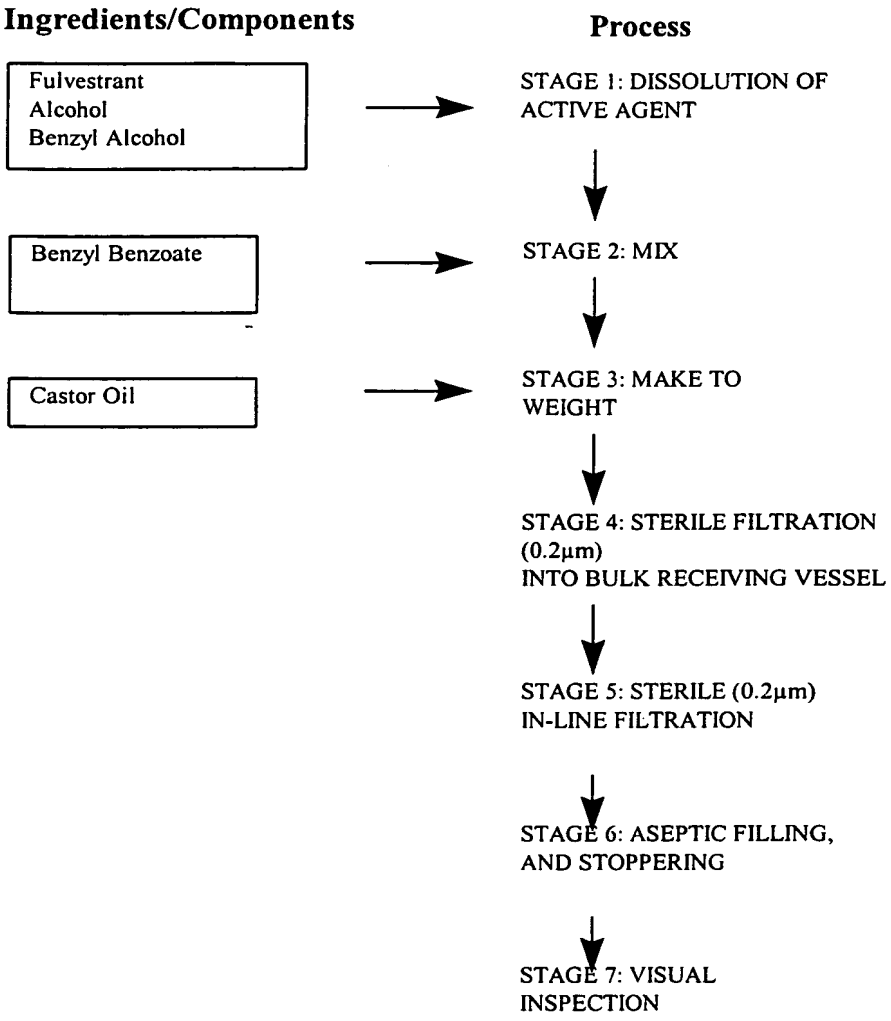
Fulvestrant is mixed with alcohol and benzyl alcohol, stirring until completely dissolved. Benzyl benzoate is added and the solution is made to final weight with castor oil and stirred, (for convenience weight is used rather than volume by using the weight to volume ratio). The bulk solution is overlaid with Nitrogen. The solution is sterilised by filtration using one or two filters of 0.2μm porosity. The sterile filtrate is kept under a nitrogen overlay as it is filled under aseptic conditions into washed and depyrogenised, sterile primary containers, for example vials or pre-filled syringes. An overage is included in the primary pack to facilitate removal of the dose volume. The primary packs are overlaid with sterile nitrogen, before aseptically sealing.

See also process flow diagram below

Quantities of each component of the formulation is choosen according to the required formulation specification, examples are described above. For example quantities are added of each component to prepare a formulation which contains

10% weight per volume of benzyl alcohol
10% weight per volume of ethanol
15% weight per volume of benzyl benzoate
250mg of fulvestrant for each 5ml of finished formulation
and the remaining amount as castor oil

FLOW DIAGRAM OF MANUFACTURING



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2. Wakeling AE. Novel pure antioestrogens: mode of action and therapeutic prospects. American New York Academy Science 1990a; 595: 348-56.

3. Wakeling AE. Steoidal pure antioestrogens. In Lippman M, Dickson R, editors. Regulatory mechanisms in breast cancer. Boston: Kluwer Academic, 1990b: 239-57.

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5. Wakeling AE, Bowler J. Steroidal pure antioestrogens. Journal Endocrinology 1987; 112: R7-10.

6. Wakeling AE, Bowler J. Biology amd mode of action of pure antioestrogens. Journal Steroid Biochemistry 1988; 3: 141-7.

Claims

1. A pharmaceutical formulation adapted for intra-muscular injection comprising fulvestrant, 25% or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 10% weight of benzyl benzoate per volume of formulation and a sufficient amount of a ricinoleate vehicle, taking into account the addition of any further optional pharamaceutically-acceptable excipients, so as to prepare a formulation of at least 45mgml^{-1} of fulvestrant.

2. A pharmaceutical formulation as claimed in claim 1 which contains 22% w/v or less of a pharmaceutically-acceptable alcohol.

3. A pharmaceutical formulation as claimed in claim 1 which contains 20% w/v or less of a pharmaceutically-acceptable alcohol.

4. A pharmaceutical formulation as claimed in claim 1 which contains and 18%w/v or less of a pharmaceutically-acceptable alcohol.

5. A pharmaceutical formulation as claimed in any claim from 1 to 4 which contains 60% w/v or less of benzyl benzoate.

6. A pharmaceutical formulation as claimed in any claim from 1 to 4 which contains 50%w/v or less of benzyl benzoate.

7. A pharmaceutical formulation as claimed in any claim from 1 to 4 which contains 45% w/v or less of benzyl benzoate.

8. A pharmaceutical formulation as claimed in any claim from 1 to 4 which contains 40% w/v or less of benzyl benzoate.

9. A pharmaceutical formulation as claimed in any claim from 1 to 4 which contains 35% w/v or less of benzyl benzoate.

10. A pharmaceutical formulation as claimed in any claim from 1 to 4 which contains 30% w/v or less of benzyl benzoate.

11. A pharmaceutical formulation as claimed in any claim from 1 to 4 which contains 25% w/v or less of benzyl benzoate.

12. A pharmaceutical formulation as claimed in any claim from 1 to 11 wherein the total volume of the formulation is 5ml, or less, and the concentration of fulvestrant is at least $45mgml^{-1}$.

13. A pharmaceutical formulation as claimed in any claim from 1 to 11 wherein the total amount of fulvestrant in the formulation is 250mg, or more, and the total volume of the formulation is 5ml, or less.

14. A pharmaceutical formulation as claimed in claim 13 wherein the total amount of fulvestrant in the formulation is 250mg and the total volume of the formulation is 5ml.

15. An extended release pharmaceutical formulation adapted for intramuscular injection comprising fulvestrant, 25% or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 10% weight of benzyl benzoate per volume of formulation and sufficient amount of a ricinoleate vehicle, taking into account the addition of any further optional pharmaceutically-acceptable excipients, so as to prepare a formulation of at least $50mgml^{-1}$ of fulvestrant.

Application No: _____

Pillsbury Madison & Sutro

Inventor: J. EVANS et al

Filed: 1/9/01

Client & Ref. #: ASTRAZENECA (PHM70635/US)

CL.# 9901 M# 27550 7